REMARKS

Claims 28-43, 45-47, 49-59, and 61 are pending. Claims 1-27, 44, 48, and 60 are canceled.

Claim 28 has been amended to incorporate "the substrate's entire surface", "in a flow cell", and "by flowing a purging fluid across said entire surface of said substrate in a manner sufficient to produce a stratified fluid interface that moves across said surface."

Claim 56 has been amended to incorporate "the substrate's entire surface", "in a flow cell", and "by flowing a purging fluid in a manner sufficient to produce a stratified fluid interface that moves across said surface."

Support for these amendments may be found throughout the specification, for example, on page 32, lines 4 to 29, and in Claims 44 and 48, as previously presented.

Claims 45 and 53 have been amended to change the dependency to Claim 1.

No new matter is added.

In view of the following remarks, the Examiner is requested to withdraw the rejections and allow Claims 28-43, 45-47, 49-59 and 61 the only claims pending and currently under examination in this application.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of co-pending applicationw in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention that a response to a non-final Office Action was mailed on September 17, 2008 in co-pending U.S. Patent Application No. 11/234,701.

The Applicants wish to bring to the Examiner's attention that a response to a final Office Action was mailed on October 3, 2008 in co-pending U.S. Patent Application No. 10/813,337.

The Applicants wish to bring to the Examiner's attention that a response to a final Office Action was mailed on September 22, 2008 in co-pending U.S. Patent Application No. 10/813,331.

These documents are available on PAIR, and thus are not provided with this communication.

Claim Rejections - 35 USC § 103 Gamble and Anderson

Claims 28-36, 38-44, 46-47, 49, 50, 54-56 and 61 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble et al. (USPN 5,981,733), in view of Anderson et al. (USPN 5,186,824). The Applicants traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. S*ee, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all elements were known in the prior art, the Office must also articulate a reason for combining the elements. See, *e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) citing *KSR*. Further, the Supreme Court in *KSR* also stated that that "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR* at 1740. As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

As best understood by the Applicants, the Examiner believes that combining Gamble's method of synthesizing an addressable array and Anderson's method of batch synthesis renders the rejected claims obvious.

For several reasons submitted below, the Applicants contend that in view of the cited references, one of skill in the art would not have arrived at the rejected

claims. For example, the cited art does not teach or suggest "displacing in a flow cell the deblocking fluid from said entire surface [...] by flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface," as required by the rejected claims.

Briefly, Gamble teaches an apparatus comprising a positioning system that moves the substrate from the printing jet to the reaction chamber in order to synthesize an addressable array. Gamble, however, is completely silent on "displacing in a flow cell the deblocking fluid from said entire surface [...] by flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface." Hence, the Examiner acknowledges that Gamble does not teach that "the wash reagents contact said entire surface of the substrate" (page 8 of Final Office Action dated 10/16/08) and cites Anderson to remedy Gamble's deficiency.

Anderson teaches a batch rotating reactor for synthesizing oligonucleotides on controlled-pore glass (CPG) beads. The internal space of the rotor holds particulate porous reaction and allows flowing liquid of increasing or decreasing density in and out of the rotor. However, since Anderson only teaches batch synthesis of oligonucleotides on CPGs, Anderson is completely silent on *in situ* fabrication of an oligonucleotide array. Without an array substrate, Anderson cannot teach or suggest "flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface."

As such, Gamble and Anderson cannot teach or suggest each and every element of Claims 28, 56, and their dependents because at least the element of "flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface" is missing.

Although none of the cited references teach or suggest each and every element of the rejected claims as discussed above, the Applicants further submit that there are additional reasons why one of ordinary skill in the art would not have combined the references in the manner proposed by the Examiner in an attempt to comport with the rejected claims. One of the reasons is that the methods of Gamble and Anderson are actually very different, the former being directed to synthesizing different moiety at discrete locations on a substrate, while the latter is directed to a batch synthesis reaction, in which there can be no fabrication of different

oligonucleotides on addressable locations. In view of these two very different methods, no teaching or suggestion is found anywhere to combine the *in situ* fabrication of Gamble with the batch synthesis of Anderson.

Another reason why one of ordinary skill in the art would not have arrived at the rejected claims is that since the rotating rotor is required for creating an interface between fluids of different density, combining Anderson's rotor and Gamble's addressable array would result in a non-functional embodiment. As such, one of ordinary skill in the art would have no reason to make the combination. Anderson's reactor rotates with a certain centrifugal speed during introduction of various fluids in and out of the rotor (column 7) so that the interface between a denser and a lighter fluid assumes the configuration of a parabola (column 12). Gamble's addressable array enclosed in Anderson's rotor would subject the array to a centrifugal force that could not only damage the array but would also render *in situ* fabrication impossible. Accordingly, one of ordinary skill in the art would not have combined Anderson and Gamble to arrive at "a stratified fluid interface that moves across said surface [of an addressable array]."

Accordingly, without the hindsight provided by the Applicants, one of skilled in the art would not have combined the cited art in the manner suggested by the Examiner.

The Examiner further asserts that one of ordinary skill in the art would have been motivated to combine the references in a manner in an attempt to read onto the rejected claims because of washing efficiency, quantitative replacement of solutions, and precise control of fluid flow (pages 9-10 and 22-23 of Final Office Action dated 10/16/08), allegedly espoused by Anderson as important in polymer synthesis.

Contrary to the statements the Examiner has made, there is no support that the combination would result in "washing efficiency" or that "quantitative replacement of solutions" (column 19 of Anderson) would lead one of ordinary skill in the art to arrive at the claimed invention. Gamble has stated in column 2, lines 45-48 that an "advantage of [Gamble's] device is its sparing use of reagents." As such, it is unclear how a combination of Gamble and Anderson would result in further washing efficiency. As for quantitative replacement, monitored draining of the fluid or controlled fluid flow can also accomplish a quantitative fluid flow. Drying protocols taught by Gamble (column 13, lines 6-15) may also be considered quantitative

replacement of the reagents if the fluid flow is quantitative. As such, there is no reason why a desire for quantitative replacement would necessarily lead to the rejected claims.

Lastly, the Applicants submit below another reason why one of ordinary skill in the art would not have arrived at the rejected claims. A careful consideration of the field of array synthesis reveals that the much of the teaching around the priority date of the instant application comprises drying steps in between wash steps and is completely devoid of the element of "displacing the deblocking fluid [...] with a purging fluid." Certain patents are briefly discussed below to illustrate the prevalent practice of air drying in the field of array synthesis and the lack of teaching of "displacing "deblocking fluid [...] with a purging fluid."

One such reference is Glazer et al. (USPN 6,824,866), in which the performance of an array substrate was tested by synthesizing fluorescein phosphoramidite onto the substrate. In column 22, lines 43-45 of Glazer, the substrates are "deprotected [...] and blown dry with dry nitrogen."

In Blanchard et al. (USPN 6,028,189) and Blanchard et al. (USPN 6,419,883), the methods taught in both references require "drying in a stream of dry nitrogen" in columns 12 and 38, respectively.

Schermer et al. (USPN 6,485,918) teaches an apparatus for array synthesis that performs "automatic washing and drying." The method taught by Schermer also involves jetting wash solutions and vacuum or gas-stream drying (column 8, lines 47-59).

Even Gamble, a reference cited by the Examiner, teaches that the array substrate is to be "dried with a stream of compressed gas [...] to remove any unreacted deprotect reagent" (column 13, lines 5-15).

In view of the above-cited patents, the prevalent teachings in the art of array synthesis employ air drying and are completely silent on "displacing in a flow cell the deblocking fluid [...] by flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface." As such, without the hindsight provided by the Applicants' application, one of ordinary skill in the art would not have any reason to combine Gamble's and Anderson's teachings in the manner suggested by the Examiner to arrive at the rejected claims.

Not only is there no reason for one of ordinary skill in the art to combine the

references in the manner suggested by the Examiner, but even if the references are combined in an attempt to read onto the rejected claims as suggested by the Examiner, they also cannot establish a *prima facie* case of obviousness. This is because the proposed modification would either change the principle of operation of the methods taught by the references or render them inoperable.

Under current law, such logic cannot be used to establish a *prima facie* case of obviousness. It is well established that a reference cannot render an invention obvious

> if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified...[1]
> or
> if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose.[2]

As noted above, to follow Anderson's teachings, one of ordinary skill in the art would resort to a rotating rotor while introducing fluids sequentially in increasing density to achieve the "stratified fluid interface," as required by Claim 1. However, combining such rotating rotor with the *in situ* fabrication of Gamble in order to achieve "a stratified liquid interface [...] moves across said surface [of the array substrate]," one would end up having an addressable array inside a rotating rotor. The substrate of the addressable array may be damaged while experiencing centrifugal force inside Anderson's rotor. Since a glass bead is not an addressable array nor can an addressable array exist in suspension, it would render either Gamble's method or Anderson's method inoperable.

In view of the foregoing discussion, the Applicants submit that the rejected claims are not obvious for at least the following reasons. First, not all elements of the rejected claims are taught or suggested by the cited references. Specifically, the elements of "displacing in a flow cell the deblocking fluid [...] by flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface" cannot be taught or suggested by the cited art. Second, the

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[1] *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP 2143.01 VI
[2] *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP 2143.01 V

Examiner has fails to articulate a reason to combine or modify the cited references to arrive at all the elements of Claims 1 and 56. Without the hindsight provided by the instant application, there would be no reason to modify the references in the manner suggested by the Examiner. Third, considering the art around the priority date of the instant application, it is apparent that the prevalent teaching involves methods that do not displace deblocking fluid with a purging fluid. Lastly, the cited references also cannot teach or suggest the Applicants' claimed invention because the combination of the cited references would, at best, only lead one of ordinary skill in the art to enclose Gamble's substrate in a centrifugal rotor and such an attempt to modify the teachings of the cited references to comport with the rejected claims would either render the combination inoperable or change the original principle of operations. As such, Gamble alone or in combination with Anderson cannot render the rejected claims obvious.

Accordingly, Claims 28-32, 34-36, 38-43, 46-47, 50, 54-55 and 61 are not obvious under 35 U.S.C. § 103(a) over the cited combination of Gamble, in view of Anderson The Applicants thus respectfully request that this rejection be withdrawn.

Claim Rejections - 35 USC § 103 Gamble, Anderson, and Greene

Claim 37 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble et al. (USPN 5,981,733), in view of Anderson et al. (USPN 5,186,824), and further in view of Greene et al. (*Protective Groups in Organic Synthesis*, 3rd ed., Wiley and Sons, New York, 1999, page 106).

As discussed above, Gamble and Anderson cannot be combined to support a *prima facie* case of obviousness because, *inter alia*, there is no reason for one of ordinary skill in the art to modify Gamble without the hindsight provided by the Applicants. Moreover, the method would be rendered inoperable by the combination of the references.

Greene is cited solely for its alleged disclosure that the purging fluid density of Anderson is higher than the deblocking fluid density taught by Greene. As such, Greene fails to remedy the deficiencies discussed above. Accordingly, Claim 37 is not obvious over the cited combination of Gamble in view of Anderson, and in further view of Greene, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Gamble, Anderson, and Mian

Claim 45 is rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble et al. (USPN 5,981,733), in view of Anderson et al. (USPN 5,186,824), and further in view of Mian et al. (U.S. Patent No. 6,319,469).

As reviewed previously, Gamble and Anderson cannot be combined to support a *prima facie* case of obviousness because, *inter alia*, there is no reason for one of ordinary skill in the art to modify Gamble without the hindsight provided by the Applicants. Moreover, at least one method would be rendered inoperable by the combination of the references.

Mian is cited solely for its alleged disclosure of flow rate of purging fluid and as such, cannot remedy the deficiencies of Gamble and Anderson. Although the rejection of Claim 45 may be withdrawn on this basis alone, the Applicants further submit that the combination of Mian with Gamble and Anderson would not result in the rejected claims. Briefly, Mian teaches moving fluid on a rotatable disc in defined microchannels by the centripetal force arising from the rotation. The disc contains reaction chambers in which PCR, immunoassay, restriction digestion, etc., may take place. The Examiner has not articulated how flowing fluids in microchannels as taught by Mian may be combined with the batch synthesis of Anderson and *in situ* fabrication of Gamble's array to render Claim 45 obvious. As such, it is not clear how one of ordinary skill in the art could combine Mian with Gamble and Anderson to arrive at the rejected claim.

Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Gamble, Anderson, and Bass

Claims 48, 51, and 52 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble et al. (USPN 5,981,733), in view of Anderson et al. (USPN 5,186,824), and further in view of Bass et al. (U.S. Pub. No. 2003/0003222).

In making this rejection, the Examiner acknowledges that Gamble and Anderson do not teach that the array substrate of Gamble is placed within a flow cell for the displacing step (page 30 of Final Office Action dated 10/16/08). The Examiner then cites Bass in an attempt to remedy this deficiency of Gamble and Anderson.

As explained above, Gamble and Anderson cannot be combined to support a *prima facie* case of obviousness because, *inter alia*, there is no reason for one of ordinary skill in the art to modify Gamble without the hindsight provided by the Applicants. Moreover, the method would be rendered inoperable by the combination of the references.

As for Bass, the Examiner asserts that one of ordinary skill in the art would have modified Gamble to place the array substrate in a flow cell for the displacing or deblocking step as taught by Bass. The Applicants submit that even if Gamble were to be modified to have an array substrate in a flow cell for the displacing step, this combination is still missing the step of "displacing in a flow cell the deblocking fluid from said entire surface [...] by flowing a purging fluid [...] in a manner sufficient to produce a stratified fluid interface that moves across said surface." The Applicants submit that one of ordinary skill in the art would not have arrived at the rejected claims in view of Gamble, Anderson, and Bass.

Since the fluid displacement taught by Anderson occurs in a rotating rotor, there can be no teaching or suggestion to perform the method of fluid displacement in a "flow cell," as recited in the rejected claims. Specifically, nowhere in Anderson is there a flow cell in which an array substrate may be mounted or a flow cell in which there is a "stratified fluid interface," as required by the rejected claims. As such, it is unclear as to how one of ordinary skill in the art could use Anderson's fluid displacement method in a flow cell in order to comport with Gamble's method of array synthesis and Bass's flow cell.

As such, Bass fails to make up the deficiencies discussed above. Accordingly, Claims 51 and 52 are not obvious over the cited combination of Gamble, Anderson and Bass, and the Applicants respectfully request that the rejection be withdrawn.

Claim Rejections - 35 USC § 103 Gamble, Anderson, and Farr

Claim 53 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Gamble et al. (USPN 5,981,733), in view of Anderson et al. (USPN 5,186,824), and further in view of Farr (U.S. Patent No. 3,969,250).

As explained above, Gamble and Anderson cannot be combined to support a *prima facie* case of obviousness. As Farr was cited solely for the asserted teaching

of the stratification of liquids using a pressure gradient, Farr fails to make up for the above deficiencies.

Although the rejection of Claim 53 may be withdrawn on this basis alone, the Applicants further submit that there is no reason for Farr to be combined with Gamble and Anderson. According to the passages cited by the Examiner (column 1, lines 5-10 and column 2, lines 24-26), Farr teaches a plunger assembly used to isolate the supernatant of a blood serum that has been stratified by centrifuging or standing in a test tube. Since Farr's teaching of a stratified blood supernatant in a test tube is completely unrelated to array synthesis, it is unclear of how stratifying blood samples would lead one of ordinary skill in the art to arrive at "a pressure gradient [...] used to produce the stratified interface" "that moves across said surface [of the array substrate]," as required by the rejected claim.

The Examiner further asserts that it would have been obvious to make the combination because of "the added advantage of minimizing labor and possible contamination of the samples as taught by Farr (column 2, lines 24-26)" (page 33 of Final Office Action dated 10/16/08). However, the Applicants submit that the Examiner has misconstrued the advantage taught by Farr. When the cited passage is read in context, it is clear that the advantage discussed by Farr is due to the "telescoping of the plunger into the packed cell mass in the parent blood tube," and not due to stratification by a pressure gradient. Accordingly, the Examiner has failed to articulate a reason for one of ordinary skill in the art to combine Farr with Gamble and Anderson in an attempt to comport with the rejected claim.

As such, Claim 53 is not obvious over Gamble, in view of Anderson, and further in view of Farr, and this rejection may be withdrawn.

CONCLUSION

In view of the amendments and remarks above, the Applicants respectfully submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 327-3400.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 and 1.17 which may be required by this paper, or to credit any overpayment, to Deposit Account No. 50-1078.

Respectfully submitted,

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